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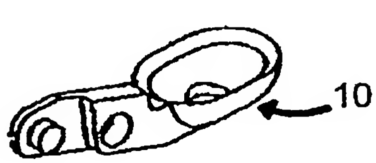
(54) Title: RADIOPAQUE SURGICAL IMPLEMENT



(57) Abstract: X-ray imageable articles, for instance surgical implements or parts therefore which are used in minimally invasive surgical procedures, may be prepared by a process including the steps of: (a) preparing a mixture composiiton comprising: i)radiolucent particulate material selected from ceramic materials metallurgic materials, and combinations thereof and having a particulate size of no more than 40 microns, ii) radiopaque particulate material selected from ceramic materials, metallurgic materials, and combinations thereof and having a particulate size of no more than 40 microns, and (iii) at least one polymeric binder material; (b) injection molding the mixture composition into a preform; (c) optionally removing the binder material from the preform; and (d) sintering the perform.

RADIOPAQUE SURGICAL IMPLEMENT

BACKGROUND OF THE INVENTION

This invention relates to medical devices which are inserted into the body and located by X-ray imaging.

Various types of minimally invasive surgical techniques have been developed in recent years in which catheters or similar devices are used to convey a operative implement through a body passage, including such passages as the blood vessels, gastrointestinal tract, urethral and urethral tracts, bronchial and esophageal tracts, to a specific location where the implement is operatively employed or delivered. Catheters are used to perform balloon angioplasty, to deliver and lodge stent devices, to deliver drugs, to abrade or volatilize lesions, to remove temporary, misplaced or dislodged stents, and the like. For such activities, X-ray imaging is often used to follow the catheter or the operative implement as it traverses the body channel and/or to monitor the actual employment or deployment of the implement.

For materials which are transparent to X-ray, or are only weakly radiopaque, it has been conventional to provide radiopaque marker bands, coatings or laminates of more intensely radiopaque materials on the devices or implements in order to achieve the necessary contrast for a readily observable image.

A number of the implements, used or delivered by such techniques, or parts thereof may be made of metal or ceramic materials. Traditionally such implements are, or are made up of, small complex machined parts. Stents are an example of such an implement which is typically made by machining metal.

A technique which is known for manufacturing metal and ceramic parts utilizes injection molding and sintering of composite formulations. This technique, designated "CIM" for ceramic articles and "MIM" for metal articles utilizes formulations which are mixtures of a resinous binder material and a very fine powder of the respective ceramic or metal material, which is injection molded to produce a desired shaped article, the molded article typically being somewhat larger than the desired size. The binder is then typically removed by extraction, heating, or both, leaving a shaped

structure of the powder material. This structure is sintered to form the final article, typically shrinking by a reproducible amount.

Similar products can be prepared from combining ceramic materials with metallurgic materials to form what is known as a "cermet."

A porous stent formed by a powdered metal sintering process is disclosed in US 5972027, incorporated herein by reference in its entirety. A perfusion tip for an ablation catheter is described in US 6017338, incorporated herein by reference in its entirety.

SUMMARY OF THE INVENTION

The present invention is directed to articles which can be made using a CIM or MIM process, preferably articles which are, or are part, of surgical implement structures such as catheters, forceps, stents, perfusion heads, electrodes, and the like used in minimally invasive surgical procedures and . The invention also relates to CIM or MIM processes for preparing such implements, or parts thereof, in which the ceramic or metal powder material used to form the article comprises a radiolucent material and a radiopaque material.

In a first aspect of the present invention there is provided a method for preparing an X-ray imageable article comprising:

(a) preparing a mixture composition comprising:

i) radiolucent particulate material selected from ceramic materials, metallurgic materials, and combinations thereof and having an average particulate size of no more than 40 microns,

ii) radiopaque particulate material selected from ceramic materials, metallurgic materials, and combinations thereof and having an average particulate size of no more than 40 microns, and

(iii) at least one polymeric binder material;

(b) injection molding the mixture composition into a preform;

(c) optionally removing the binder material from the preform; and

(d) sintering the preform.

Articles, especially surgical implements comprising an article composed of a sintered mixture of radiolucent and radiopaque powders as described herein, and medical devices comprising such implements are other aspects of the invention.

A further aspect of the invention is a surgical method in which a surgical implement as described herein is carried via a catheter to a remote site within the body and used in performing a surgical procedure, wherein the article of the invention is observed fluoroscopically during at least a portion of the time it is in the body.

Still further aspects of the invention are described in the detailed description below and in the claims.

BRIEF DESCRIPTION OF THE FIGURES

Figure 2 is an orthagonal view of a ceramic tip for an RF-PMR catheter fashioned in accordance with the present invention.

Figure 1 is a perspective view of a single jaw of a biopsy forceps fashioned in accordance with the present invention.

Figure 3 is a perspective fragmentary view of a stent fashioned in accordance with the present invention.

DETAILED DESCRIPTION

As noted above the invention is preferably practiced to prepare articles which are, or are components of surgical implements adapted for delivery and operation at a remote site within the body on a catheter.

According to the invention the subject article is composed of a mixture of at least two inorganic ceramic or metallurgic materials, one of which is radiolucent, (i.e. invisible or only weakly visible fluoroscopically), and the second of which is radiopaque (readily visible fluoroscopically).

Particulate materials suitable for the radiolucent inorganic material making up the component (i) of the moldable compositions include:

ceramic materials such as alumina, aluminum nitride, silica, silicon, silicon carbide, silicon nitride, sialon, zirconia, zirconium nitride, zirconium carbide, zirconium boride, titania, titanium nitride, titanium carbide, barium titanate, titanium

boride, boron nitride, boron carbide, magnesium oxide, calcium oxide, and the like, and combinations thereof; and

metallurigic materials including metals, and mixtures or alloys thereof such as stainless steel, iron, nickel, titanium, nitinol, and metallic oxides which can be converted to metals when sintered in a reducing environment, and combinations thereof.

Combinations of such inorganic radiolucent ceramic and metallurgic materials may also be employed as the component (i). Preferred radiolucent materials include alumina, zirconia, and 17-4 PH, MP35N, 316 LVM, and 304V stainless steels.

Particulate materials suitable for the inorganic radiopaque material making up the component (ii) of the moldable compositions include:

ceramic materials such as tungsten carbide, and tungsten boride, and

metallurgic materials such as platinum, tantalum, iridium, tungsten, rhenium gold and alloys of such metals.

Combinations of such inorganic radiopaque ceramic and metallurgic materials may also be employed as the component (ii). Preferred radiopaque materials include platinium, tungsten, rhenium and tantalum.

The morphology of the inorganic particulate materials (i) and (ii) is not critical but is preferably approximately spherical. The particle sizes of the materials will both be within the range suitable for forming sintered articles, suitably an average of about 40 micrometers (microns) or less, more preferably an average of from about 0.5 to about 10 micrometers in diameter.

The ratio of the radiolucent and radiopaque materials may vary widely, depending on the desired structural properties and radiopacity of the finished article. Generally the radiopaque material (ii) will constitute at least 2% and no more than about 75% by volume of the total volume of the components (i) and (ii). More typically, structural and/or cost factors will favor the radiolucent component, so that the radiopaque component will constitute no more than 50% by volume and preferably no more than about 35% by volume of the two. On the other hand, if too little of the radiopaque component is employed the fluoroscopic visibility of the implement may not be adequately enhanced. Consequently it will generally be desirable to employ at least

5% and often 10% or more of the radiopaque component, based on the total volume of these two components.

Also, it is generally preferred that the radiopaque material have a melting point which is not substantially lower than the radiolucent material so that fluidization of the radiopaque material does not occur before the radiolucent material reaches sintering temperature. More preferably the radiopaque material has a melting point which is about the same or is even higher than that of the radiolucent material.

The third component of the composition is a binder material (iii). Any material suitable as a binder material for CIM or MIM processes may be used. Exemplary materials include polyolefins, such as polyethylene and propylene; olefin copolymers such as ethylene vinyl acetate copolymers; poly(meth)acrylates including polymethyl methacrylate, polybutyl methacrylate and the like; polystyrene and other styrene group resins; polyvinyl chloride; polyamides; polyesters; polyethers; polyacetals; various types of wax, including paraffin; and the like. Exemplary binders are described in EP-A-0 444 475, EP-A-0 446 708 and EP-A-0 444 475, incorporated herein by reference.

The binding agents are employed in conventional amounts, generally from about 2% to about 30% by weight of the injection moldable composition. More preferably the binder will be employed in an amount of from about 4 to about 15 % by weight of the composition. Generally lower amounts of binder will be preferred to minimize shrinkage during sintering. However, with very complex shapes, if the shrinkage is carefully controlled to give good reproducibility and avoid shape distortion, high shrinkage may be advantage in allowing larger molds to be used to produce the preform.

In addition to the three components described above, various additives known in the art may be added in conventional to the moldable composition. Examples of such additives include plasticizing agents, lubricating agents, antioxidants, degreasing promotion agents, and surfactants.

The composition of the inorganic powders (i) and (ii), the binder (iii) and any other additives are suitably blended in a kneading machine above the melting point of the binder and the kneaded product pelletized before use. Alternatively any other

conventional mixing technique may be used and/or the blended mixture may be used without pelletization.

In the second step of the inventive process the composition produced as described above is injection molded into a compacted preform. The dimensions of the mold are set taking into account the shrinkage that will occur from the later sintering step. Typical molding conditions will provide the composition to the mold at a temperature above the melting point of the binder, typically from about 130-200 °C and at injection pressure of from about 30,000 to as high as 200,000 kPa. The mold temperature suitably will be below that of the composition, and below the glass transition temperature of the binder, typically from about 5°C to about 50°C. Alternatively the mold may be at a higher temperature when the composition is injected and then subsequently cooled. The preform produced in this step is then removed from the mold.

After the preform is removed from the mold a binder extraction process may be performed on the preform. In forming sintered parts it is not always necessary to remove the binder as it may vaporize/decompose during sintering. However, better dimensional stability results are often obtained if the binder is removed before the preform is sintered. Known binder removal methods include solvent extraction, thermal decomposition/vaporization at a temperature below the sintering temperature, and chemical decompositon, for instance decomposition of polyacetal resins by exposure to an acidic gas at elevated temperature. Combinations of such removal methods may also be employed . Suitable conditions for such binder extractions are known in the art.

Next, the preform, either as obtained directly from the mold or after binder extraction is heated under conditions suitable for sintering the inorganic particles of the components (i) and (ii). Typical conditions will be a temperature of from about 400°C to about 1700°C for about 10 to about 30 hours, although higher temperatures and longer or shorter times may be suitable for some articles. Typically the sintering step will be conducted in a non-oxidizing atmosphere, for example, in argon gas or other inactive gases, under a vacuum or reduced pressure conditions. In some instances, for instance where the metallurgic material is a metal oxide, hydrogen will be

provided to accomplish a reduction of such oxide to the metal during sintering. A reduction process adaptable to the present invention is described in US 6080808, incorporated herein by reference.

In some cases surface hardness or other desirable properties may be imparted to the implement by providing an atmosphere containing one or more gas(es) containing least one of C, O or N during a portion of the sintering time. Such gases may be selected from air, O_2, CO_2, CO, N_2, methane, acetylene, propane and mixtures thereof.

After sintering, the formed article may be subjected to any necessary finishing steps. For example, lubricity coatings may be applied, finishing machining may be performed, and/or surface processing may be performed such as shot blasting, honing, grinding, etching, wet plating, vacuum evaporation, ion plating, spattering, CVD, and the like.

The powder injection molding method described above allows complicated shapes to be formed monolithically with a tailored radiopacity in a simple and repeatable high production rate process.

Through adjustment of types of binding agents, added amounts, binder extraction conditions, and sintering conditions, various material properties of the inventive implement can be controlled or set. Examples of such properties include the composition of the surface layer, the pore diameter, and the number of pores.

The invention permits the radiographic contrast range of the article to be tailored to permit ready visualization, without creating an X-ray artifact which masks the surrounding vessel and tissue. This is especially important in surgical techniques practiced via catheters, since, once the article has been delivered to the site of treatment it is often necessary to visualize surrounding tissue in order to successfully perform a procedure. Still further, in the case of an implement, such as a stent, which is left in the body as a result of the procedure, it is important to monitor the tissue condition through the stent subsequent to placement to verify vessel patentcy. For this reason, the implement needs to be bright enough during X-ray fluoroscopy to be seen using an X-ray intensity which allows visualization of the surrounding tissue, but dim enough to be seen through.

Referring now to the Figures, there is shown in Figure 1 a single jaw 10 of a two-jaw biopsy forceps which may be mounted on a catheter and transported via the vascular system from a remote location to a diseased or transplanted heart and at that location deployed and operated to grab a tissue sample. The forceps is then removed from the body and the tissue sample retrieved for inspection. Such forceps jaws (T-Rex®) are now conventionally made by machining a blank of a medical grade stainless steel. When made in accordance with the present invention from a mixture of powders of a medical grade stainless steel and a radiopaque metal such as platinum or tungsten, the delivery and removal of the forceps, as well as its operation at the heart site, may be more easily monitored than if the forceps jaws are made only from machined stainless steel.

Figure 2 shows a perspective view of a ceramic tip 20 for a PMR catheter, conventionally made of alumina by a CIM process. The tip serves an an insulator and mechanical stop for an RF electrode array used to treat myocardial infarction. When made in accordance with the present invention from a mixture of powders of a medical grade alumina and tungsten or rhenium, the delivery and removal of the catheter may be easily monitored without the necessity of providing radiopaque marker bands or the like. Thus the manufacturing process is simplified and components presenting potential bonding issues are eliminated.

Figure 3 shows a porous drug delivery stent 30 of the type described in US 5972027, made from sintered stainless steel powder. When made in accordance with the present invention from a mixture of powders of a medical grade stainless steel and a radiopaque metal such as tantalum, platinum or tungsten, the delivery of the stent, and its functioning to maintain vessel patency may be more easily monitored than if the stent is made only from sintered stainless steel powder.

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiments, it is to be understood that the invention is not to be limited to the disclosed embodiments but, on the contrary, is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

The above examples and disclosure are intended to be illustrative and not exhaustive. These examples and description will suggest many variations and alternatives to one of ordinary skill in this art. All these alternatives and variations are intended to be included within the scope of the attached claims. Those familiar with the art may recognize other equivalents to the specific embodiments described herein which equivalents are also intended to be encompassed by the claims attached hereto. Further, the particular features presented in the dependent claims below can be combined with each other in other manners within the scope of the invention such that the invention should be recognized as also specifically directed to other embodiments having any other possible combination of the features of the dependent claims.

CLAIMS

1. A method for preparing an X-ray imageable article comprising:

(a) preparing a mixture composition comprising:

i) radiolucent particulate material selected from ceramic materials, metallurgic materials, and combinations thereof and having an average particulate size of no more than 40 microns,

ii) radiopaque particulate material selected from ceramic materials, metallurgic materials, and combinations thereof and having an average particulate size of no more than 40 microns, and

(iii) at least one polymeric binder material;

(b) injection molding the mixture composition into a preform;

(c) optionally removing the binder material from the preform; and

(d) sintering the preform.

2. A method as in claim 1 wherein said article is a surgical implement or component thereof, said implement adapted to be disposed on a catheter and conveyed thereon a remote site within the body and operated at such site to perform a surgical procedure.

3. A method as in claim 1 wherein said radiolucent material is selected from the group consisting of alumina, aluminum nitride, silica, silicon, silicon carbide, silicon nitride, sialon, zirconia, zirconium nitride, zirconium carbide, zirconium boride, titania, titanium nitride, titanium carbide, barium titanate, titanium boride, boron nitride, boron carbide, magnesium oxide, calcium oxide, stainless steel, iron, nickel, titanium, nitinol, and metallic oxides which can be converted to metals when sintered in a reducing environment, and combinations thereof.

4. A method as in claim 1 wherein said radiopaque material is selected from the group consisting of tungsten carbide, tungsten boride, the metals platinum,

tantalum, iridium, tungsten, rhenium and gold, alloys of said metals, and combinations thereof.

5. A method as in claim 1 wherein the radiopaque material (ii) constitutes at least 2% and no more than about 75% by volume of the total volume of the components (i) and (ii).

6. A method as in claim 1 wherein the radiolucent material is selected from the group consisting of alumina, zirconia and stainless steel and the radiopaque material is selected from the group consisting of platinum, tungsten, rhenium and tantalum, and the radiopaque material constitutes from about 10 to about 50% by volume of the total volume of the components (i) and (ii).

7. A method as in claim 1 wherein the binder component (iii) is selected from the group consisting of polyolefins; olefin copolymers such as ethylene vinyl acetate copolymers; poly(meth)acrylates; styrene group resins; polyvinyl chloride; polyamides; polyesters; polyethers; polyacetals; and waxes.

8. A method as in claim 1 wherein the binder component (iii) is employed in said mixture composition in an amount of from about 2% to about 30% by weight thereof.

9. A method as in claim 1 wherein the binder removal step c) is preformed.

10. An article comprising a sintered mixture of at least two inorganic powder materials at least one of which is a radiolucent and at least one of which is radiopaque.

11. A medical device comprising an article as in claim 10.

12. A medical device as in claim 11 wherein said device comprises a catheter and said article is a surgical implement which can be carried on the catheter to a remote site within the body.

13. A medical device as in claim 12 wherein said radiolucent material is selected from the group consisting of alumina, aluminum nitride, silica, silicon, silicon carbide, silicon nitride, sialon, zirconia, zirconium nitride, zirconium carbide, zirconium boride, titania, titanium nitride, titanium carbide, barium titanate, titanium boride, boron nitride, boron carbide, magnesium oxide, calcium oxide, stainless steel, iron, nickel, titanium, nitinol, and metallic oxides which can be converted to metals when sintered in a reducing environment, and combinations thereof.

14. A medical device as in claim 12 wherein said radiopaque material is selected from the group consisting of tungsten carbide, tungsten boride, the metals platinum, tantalum, iridium, tungsten, rhenium and gold, alloys of said metals, and combinations thereof.

15. A medical device as in claim 12 wherein the radiopaque material constitutes at least 2% and no more than about 75% by volume of the total volume of the radiolucent and the radiopaque materials.

16. A medical device as in claim 12 wherein the radiolucent material is selected from the group consisting of alumina, zirconia and stainless steel and the radiopaque material is selected from the group consisting of platinum, tungsten, rhenium and tantalum, and the radiopaque material constitutes from about 10 to about 50% by volume of the total volume of the radiolucent and the radiopaque materials.

17. A composition useful for preparing radiopaque components of a medical device structure, the composition comprising a mixture of

i) radiolucent particulate material selected from ceramic materials, metallurgic materials, and combinations thereof and having an average particulate size of no more than 40 microns,

ii) radiopaque particulate material selected from ceramic materials, metallurgic materials, and combinations thereof and having an average particulate size of no more than 40 microns, and

(iii) at least one polymeric binder material.

18. A composition as in claim 17 wherein:

the radiolucent material is selected from the group consisting of alumina, aluminum nitride, silica, silicon, silicon carbide, silicon nitride, sialon, zirconia, zirconium nitride, zirconium carbide, zirconium boride, titania, titanium nitride, titanium carbide, barium titanate, titanium boride, boron nitride, boron carbide, magnesium oxide, calcium oxide, stainless steel, iron, nickel, titanium, nitinol, and metallic oxides which can be converted to metals when sintered in a reducing environment, and combinations thereof;

the radiopaque material is selected from the group consisting of tungsten carbide, tungsten boride, the metals platinum, tantalum, iridium, tungsten, rhenium and gold, alloys of said metals, and combinations thereof;

the radiopaque material constitutes at least 2% and no more than about 75% by volume of the total volume of the radiolucent and the radiopaque materials; and.

the binder material is present in said composition in an amount of from about 2% to about 30% by weight thereof.

19. A composition as in claim 17 wherein the radiolucent material is selected from the group consisting of alumina, zirconia and stainless steel and the radiopaque material is selected from the group consisting of platinum, tungsten, rhenium and tantalum, and the radiopaque material constitutes from about 10 to about 50% by volume of the total volume of the radiolucent and the radiopaque materials.

20. A composition as in claim 17 wherein the average particle sizes of the radiolucent and radiopaque materials are from about 0.5 to about 10 micrometers.

21. A composition as in claim 17 wherein the radiopaque material has a melting point which is greater than or equal to the melting point of the radiolucent material.

22. A surgical method comprising conveying a surgical implement via a catheter to a remote site within the body, using said implement to perform a surgical procedure at said site and observing the implement fluoroscopically during at least a portion of the time it is in the body, wherein the implement comprises an article as in claim 10.

23. A surgical method as in claim 22 wherein the radiolucent and the radiopaque powder materials are present in relative amounts which renders the article bright enough during X-ray fluoroscopy to be seen using an X-ray intensity which allows visualization of the surrounding tissue, but dim enough to be seen through.

24. A method as in claim 2 wherein the radiolucent and the radiopaque powder materials are present in relative amounts which renders the article, when in the body, bright enough during X-ray fluoroscopy to be seen using an X-ray intensity which allows visualization of the surrounding tissue, but dim enough to be seen through.

25 A medical device as in claim 12 wherein the radiolucent and the radiopaque powder materials are present in relative amounts which renders the article, when in the body, bright enough during X-ray fluoroscopy to be seen using an X-ray intensity which allows visualization of the surrounding tissue, but dim enough to be seen through.

Fig 1

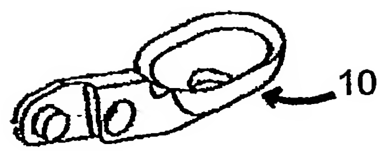


Fig 2

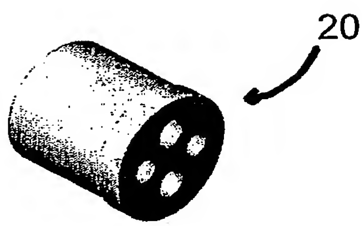
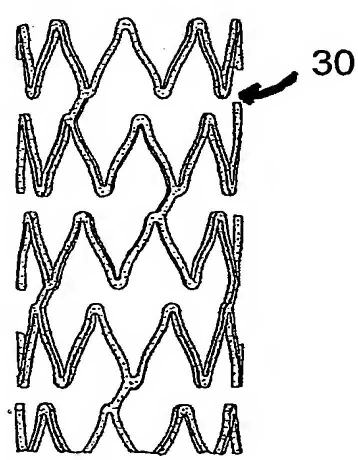


Fig 3



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(74) Agent: STEINKRAUS, Walter; Vidas, Arrett & Steinkraus, 6109 Blue Circle Drive, Suite 2000, Minnetonka, MN 55343-9185 (US).

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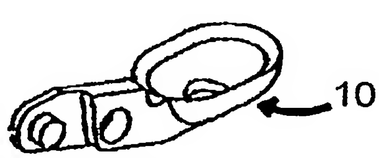
(54) Title: RADIOPAQUE SURGICAL IMPLEMENT



(57) **Abstract:** X-ray imageable articles, for instance surgical implements or parts therefore which are used in minimally invasive surgical procedures, may be prepared by a process including the steps of: (a) preparing a mixture composiiton comprising: i)radiolucent particulate material selected from ceramic materials metallurgic materials, and combinations thereof and having a particulate size of no more than 40 microns, ii) radiopaque particulate material selected from ceramic materials, metallurgic materials, and combinations thereof and having a particulate size of no more than 40 microns, and (iii) at least one polymeric binder material; (b) injection molding the mixture composition into a preform; (c) optionally removing the binder material from the preform; and (d) sintering the perform.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 462 512 A (LEE HOWARD G) 27 December 1991 (1991-12-27) column 1, line 3 - line 37 column 6, line 28 - line 34 claim 9 ---	1-25
A	US 5 972 027 A (JOHNSON MICHAEL W) 26 October 1999 (1999-10-26) cited in the application column 2, line 39 - line 56 column 4, line 64 -column 5, line 19 ---	1-25
A	EP 0 423 509 A (GEN ELECTRIC) 24 April 1991 (1991-04-24) page 2, line 19 - line 21 claims 1-4 --- -/--	1-10, 17-21,24

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 September 2002	17/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Heck, G

Int(nal Application No
PCT/US 01/47120

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 54075 A (PENN STATE RES FOUND) 28 October 1999 (1999-10-28)	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/47120

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 22 and 23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/47120

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 0462512	A	27-12-1991	US	5088927	A	18-02-1992
			AT	137781	T	15-05-1996
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WO 9954075	A	28-10-1999	AU	3569299	A	08-11-1999
			WO	9954075	A1	28-10-1999
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